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Rheumatic disorders developed after hepatitis B vaccination

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Abstract

Objective. To obtain an overview of rheumatic disorders occurring after hepatitis B vaccination.

Methods. A questionnaire was sent to rheumatology departments in nine French hospitals. Criteria for entry were rheumatic complaints of 1 week's duration or more, occurrence during the 2 months following hepatitis B vaccination, no previously diagnosed rheumatic disease and no other explanation for the complaints.

Results. Twenty-two patients were included. The observed disorders were as follows: rheumatoid arthritis for six patients; exacerbation of a previously non-diagnosed systemic lupus erythematosus for two; post-vaccinal arthritis for five; polyarthralgia-myalgia for four; suspected or biopsy-proved vasculitis for three; miscellaneous for two.

Conclusions. Hepatitis B vaccine might be followed by various rheumatic conditions and might trigger the onset of underlying inflammatory or autoimmune rheumatic diseases. However, a causal relationship between hepatitis B vaccination and the observed rheumatic manifestations cannot be easily established. Further epidemiological studies are needed to establish whether hepatitis B vaccination is associated or not with an incidence of rheumatic disorders higher than normal.

KEY WORDS: Hepatitis B vaccine, Adverse effects, Arthritis, Polyarthrititis, Rheumatoid arthritis, Lupus erythematosus, Vasculitis.

Hepatitis B vaccine was initially recommended for adults or children at high risk of hepatitis B virus (HBV) infection [1]. However, since vaccination programmes had not been effective in reducing the incidence of HBV infection, immunization strategies including universal immunization of infants were developed [2-4]. Both plasma-derived and recombinant hepatitis B vaccines are safe to administer to adults and children. The side-effects are usually minor, including headache, injection site pain, tiredness, fever, arthralgia [5-11]. These reactions usually resolve within 24-48 h. Serious adverse effects are rare [5-11]. However, medical and public interest in the safety of hepatitis B vaccination was recently heightened by medical journals and media reports of adverse effects. Some authors have described

cases of various diseases occurring after hepatitis B vaccination, such as occlusion of the central retinal vein [12], uveitis [13], lichen ruber planus [14], erythema multiforme [15], nephrotic syndrome [16], acute cerebellar ataxia [17], central nervous system demyelination [18] and transverse myelitis [19]. A few cases of rheumatological manifestations have been reported [20-32]. However, it is difficult to know whether there is a coincidental or a causal relationship between immunization and the observed manifestations. This paper reports our experience of a larger series of 22 patients. The aim of our work was not to assess whether hepatitis B immunization is associated or not with an incidence of rheumatic disorders higher than normal, but to obtain an overview of articular problems that might occur after such a vaccination. Some aspects of a single case have previously been published as a case report [33]. This observation has, however, been included in the series.

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Methods

In 1997, a questionnaire about rheumatic complaints following hepatitis B vaccination was sent to the rheumatology departments of the hospitals in Besançon, Bourg en Bresse, Chalon sur Saone, Dijon, Grenoble, Pierre Bénite, Reims, Saint Etienne and Strasbourg (France). Criteria for entry were any rheumatic complaints of 1 week duration or more, occurrence of the complaints during the 2 months following hepatitis B vaccination, no previously diagnosed rheumatic disease and no other explanation for the occurrence of complaints. The participating hospitals were given no indication as to the time period of interest. The clinical and laboratory data from all patients were collected and analysed retrospectively.

Results

Twenty-two patients were included. There were three males and 19 females, mean age 31.5 ± 12.4 (S.D.) yr (range 15–53 yr). All patients received recombinant hepatitis B vaccine between 1992 and 1997. Two were given several vaccines (hepatitis A and hepatitis B for one patient; hepatitis B, rubeola and typhoid for the other). Among the 22 cases, eight developed symptoms after the first vaccine dose, five after the second dose, three after the third dose (1 month between two injections) and six after a booster injection. The last six patients had not complained of adverse events after the previous injections. For 10 patients, the next hepatitis B vaccine inoculation was performed despite the complaints. The complaints worsened in eight cases and were not modified in one (the effects of the new injection are unknown for the last patient). The time interval between the vaccination and the occurrence of complaints was ≤ 1 week for nine patients, between 1 week and 1 month for 10 patients, and 2 months for three patients. Owing to the retrospective analysis, the laboratory investigations for differential diagnosis were performed according to the complaints, and were not the same for all patients. In particular, extensive serological tests were not performed in all cases. A summary of cases is given in Table 1.

Rheumatoid arthritis (RA)

Six women developed an inflammatory polyarthritis satisfying the 1987 ARA criteria for the diagnosis of RA. They had received immunization 1, 2, 3, 10, 18 and 20 days, respectively, prior to symptom onset. All received another injection. The symptoms worsened in four cases, and were not modified in one (the effects of the next injection were unknown for the last patient). The follow-up is now 6, 5, 3, and 2 yr, and 20 and 6 months, respectively. The affection is still persisting. During the follow-up, all patients were treated with at least one disease-modifying anti-rheumatic drug (DMARD), including methotrexate for four. Joint erosions occurred in three out of the five patients followed up for > 1 yr.

Systemic lupus erythematosus (SLE)

Two women developed exacerbation of SLE. The first patient presented with an arthritis of the right ankle occurring 1 week after immunization. The blood cell count showed moderate neutropenia (1800) and lymphopenia (1300). The tests for antinuclear antibodies (ANA) on Hep-2 cells (1:640) and for anti-SSA antibodies were positive. She had no anti-double-stranded (ds) DNA. The second patient presented with thrombocytopenic purpura occurring 1 month after the third injection of the vaccine series. The tests for ANA (1:1280), anti-dsDNA, anticardiolipin and anti-SSA antibodies were positive. In both patients, the affection was probably present prior to the vaccination: the first had a 4 yr history of photosensitivity; the second had a 2 yr history of migratory polyarthralgia.

'Post-vaccinal' arthritis

Five women developed 'post-vaccinal' arthritis. The distribution of arthritis was heterogeneous: symmetrical polyarthritis in the first patient, right and left metacarpophalangeal joints in the second patient, monoarthritis of the knee in the third patient, and asymmetrical migratory oligoarthritis predominating in the lower limb in the last two patients. In three cases, a further vaccine injection was performed, resulting in all cases in worsening of the complaints. The patients were all treated with non-steroidal anti-inflammatory drugs (NSAIDs). For two of them, the complaints regressed completely. In a third patient, the complaints regressed under NSAIDs, but she still complained of moderate arthralgia after 3 months of therapy. For the two other patients, classical NSAIDs proved ineffective and were discontinued. For the first, treatment with prednisone (1 mg/kg/day) resulted in a dramatic improvement. During the next 6 months, the dose of prednisone was progressively diminished. At this time, the treatment was discontinued. No recurrent attack occurred during the follow-up (3 yr). For the last patient, treatment with phenylbutazone resulted in some improvement, but the arthritis persisted for 5 months. At the present time, 15 months after initiation of phenylbutazone, she complains of arthralgia, but the arthritis has regressed. Consequently, a characteristic outcome in all these patients was that the arthritis regressed, although some were left with arthralgia.

Arthralgia, myalgia

Four patients suffered from polyarthralgia and myalgia, and three of them from fatigue. The complaints persisted for 2 months in the first patient and 1 yr in the second one, and then disappeared. In the third patient, the complaints have persisted for 3 months, but are now improving. In the last patient, the complaints persisted for 13 months. The patient was then lost to follow-up.

Suspected or proven vasculitis

One patient developed a biopsy-proven vasculitis, and two others developed manifestations suggesting vasculitis, but no biopsy was performed for confirmation. The

TABLE 1. Summary of cases

Rheumatic disorder	No. of patients	Age and gender	Nature of vaccine injection	Time interval between vaccination and occurrence of complaints	Effects of a new injection of hepatitis B vaccine	Laboratory tests	Follow-up
RA	6	6 females, mean age = 36.2 yr \pm 7.9 s.d. (range 25-45)	First injection: 6/6	Mean = 9 days \pm 8.4 s.d. (range 1-18)	*3: worsening after a 2nd and a 3rd injection. *1: worsening after a 2nd injection, *1: complaints not modified, *1: effects unknown	RF +: 4/6, ANA +: 4/5, HLA DR4 +: 3/3	6 and 20 months, 2, 3, 5 and 6 yr: affection persisting in all
SLE	2	2 females, aged 19 and 23 yr	Second injection: 1, third injection: 1	1 week and 1 month	1: ND, 1: worsening after the third injection	ANA and anti SSA +: 2/2, anti-dsDNA and anticardiolipin +: 1/2	2 yr in both: affection still persisting
Post-vaccinal arthritis	5	5 females, mean age = 18.8 yr \pm 4.8 s.d. (range 15-27)	First injection: 1, second injection: 2, booster injection: 2, including 1 associated with hepatitis A and 1 with rubella and typhoid	2 and 12 days, < 1 month, 1 and 2 months	3 patients (second, third and booster injection), worsening in all	RF +: 1/5, ANA +: 2/5, ESR = 20, 43, 49, 56 and < 10 mm/h, HLA B27 +: 2/4	*3: regression within 2, 8 and 12 months, no recurrent attack during follow-up (2 and 14 months, 3 yr) *1: arthralgia after 3 months *1: arthralgia after 17 months
Arthralgia-myalgia-fatigue	4	3 females, 1 male, mean age = 39.5 yr \pm 7.2 s.d. (range 33-48)	First injection: 1, third injection: 1, booster injection: 2	1 and 3 weeks, < 1 month, 2 months	ND	RF and ANA -: 3/3 ESR: 8, 20 and < 10 mm/h, CPK within normal limits: 3/3	*2: regression within 2 and 12 months, no recurrent attack during follow-up (1 and 3 yr) *1: complaints under improvement after 3 months *1: persistence after 13 months
Vasculitis (suspected or proved)	3	3 females, aged 17, 20 and 49 yr	Second injection: 1 third injection: 1 booster injection: 1	1 and 2 weeks, 2 months	ND	RF +: 1/3, ANA +: 0/3, CIC +: 1/3, cryoglobulins +: 2/3, CRP = 21, 44 and 190 mg/l	Regression within 10 days to a few weeks, no recurrent attack during the follow-up (1, 2 and 3 yr)
Oligoarthritis, erythema nodosum	1	Male, 43 yr old	Booster injection	1 week	ND	RF, ANA, CIC, cryoglobulins -, ESR = 35 mm/h, CRP = 17 mg/l	Regression within 1 month, no recurrent attack during the follow-up (18 months)
Polyarthralgia, talsalgia, sicca syndrome	1	Male, 53 yr old	Second injection	< 1 week	ND	RF and ANA -, ESR = 4 mm/h, CRP = 2 mg/l	4 months: persistence of moderate arthralgia

ND: not done.

clinical manifestations were: polyarthrititis, pain in the cervical column, myalgia, skin rash with vesicle (leucocytoclastic vasculitis on skin biopsy), low-grade fever (38°C) for one patient; polyarthrititis, abdominal pain, urticaria, low-grade fever (37.8°C) for another patient; pain in the cervical column and mental nerve neuropathy, followed by low-back pain, arthralgia and paraesthesiae of the lower limbs for the last patient. The complaints regressed rapidly under NSAIDs (two patients) or spontaneously (one patient).

Miscellaneous

A 43-yr-old man developed fever (38°C), erythema nodosum and oligoarthritis of the inferior limbs. He was treated with NSAIDs. The complaints regressed within 1 month.

A 53-yr-old man complained of migratory inflammatory polyarthralgia, talalgia, and sensation of dry eyes and mouth. He was referred to an ophthalmologist, who demonstrated sicca syndrome (Rose Bengal test), and was successfully treated with NSAIDs. Four months later, he was well, with persistence of moderate arthralgia. In particular, the sensation of dry eyes and mouth had regressed. Unfortunately, he was not referred to an ophthalmologist at this time, and was then lost to follow-up.

Discussion

Rheumatic disorders described after hepatitis B immunization

Some observations suggest that hepatitis B vaccine might be followed by various rheumatic conditions. These conditions can be put together in two groups: transient conditions, such as vasculitis, post-vaccinal arthritis, erythema nodosum; and onset or relapse of rheumatic (RA, lupus erythematosus, spondyloarthropathies, etc.) or non-rheumatic (multiple sclerosis, etc.) chronic diseases.

At least 20 cases of patients satisfying the 1987 ARA criteria for the diagnosis of RA have been described (including ours) [24, 26, 28, 30, 31]. The patients were five men and 15 women, aged from 20 to 58 yr. The onset of symptoms occurred within 1–30 days following the vaccination. Despite the arthritis, nine patients received a new injection of vaccine. The arthritis worsened in six and was unchanged in one. The effects of the new injection are unknown in the two others. The tests for rheumatoid factor (RF) were positive in 10 out of 13 patients. HLA testing showed the presence of DR1 and/or DR4 antigen in 14 out of 16 patients. During the evolution, at least 12 patients needed DMARDs, and joint erosions or periarticular osteoporosis occurred in 10 (data not known for some patients). These data suggest that there is apparently no difference between cases of RA following hepatitis B vaccination and other RA. This is in accordance with results from Harrison *et al.* [34], who suggested that patients who develop inflammatory polyarthrititis, especially RA, after various immunizations (tetanus toxoid,

influenza vaccine and miscellaneous) are clinically indistinguishable from other patients with inflammatory polyarthrititis.

A few cases of onset or reactivation of SLE after vaccination against hepatitis B have been described [25, 35, 36]. The onset of symptoms occurred within 5 days–1 month after the immunization. Two patients had a lupus nephritis (associated in one with fever and arthralgia), one patient had pericarditis, one had thrombocytopenic purpura. For all patients, the tests for ANA were positive. The evolution was favourable in all after therapy using corticosteroids and, in one, on cyclophosphamide.

Several cases of reactive arthritis following hepatitis B vaccination have been reported [20, 22, 26, 32]. Some reports of Reiter's syndrome [23] and psoriatic arthropathy [27] can probably or possibly be added to these cases. The symptoms were often controlled with NSAIDs, but sulphasalazine was sometimes needed. The complaints frequently regressed after a few months.

We observed four patients with myalgia and polyarthralgia, and, in three of them, fatigue following hepatitis B vaccination. These manifestations can be connected to the chronic fatigue syndrome. A few years ago, an independent working group agreed that there was no evidence of a cause-effect relationship between hepatitis B vaccine and chronic fatigue syndrome [37]. However, the number of patients followed up may have been too small to detect a slight increase in the relative risk.

Various other conditions following hepatitis B vaccination have been described. They include erythema nodosum and polyarthrititis [21], erythema nodosum with arthralgia and Takayasu's arteritis [38], vasculitis [39–41], polyarthrititis associated with hypercalcaemia and lytic bone lesions [29]. In most cases, the complaints were treated with NSAIDs or steroids, persisted for a few days, weeks or months, then regressed without recurrence. In our series, we observed one case of erythema nodosum with oligoarthritis and one case of vasculitis confirmed by skin biopsy. Two other patients developed manifestations suggesting vasculitis, but biopsies were not performed to confirm it. In all cases, the manifestations regressed spontaneously, or under NSAIDs or steroids, and did not recur.

Several pathogenetic models can be put forward to explain rheumatic disorders following hepatitis B vaccination. Transient conditions might be due to deposition within the synovium of circulating immune complexes containing viral antigen and anti-HBs antibodies, such as observed in some hepatitis B infections, or they might be due to hypersensitivity to some components of the vaccine, such as thimerosal [42, 43] or yeast proteins [44]. Onset of chronic inflammatory or autoimmune diseases might be due to molecular mimicry or to post-immunization conditions indistinguishable from individualized diseases. The diversity of the observed diseases is not in favour of these hypotheses. A more attractive hypothesis is that hepatitis B immunization might trigger the onset or the relapse of the

diseases in individuals with underlying genetic and immunological susceptibility [34].

Coincidental or causal relationship?

However, it is difficult to know whether there is a coincidental or a causal relationship between immunization and the observed rheumatic manifestations. Our work was an observational retrospective study, and was not performed to respond to this question. Since the investigations performed for differential diagnosis were not the same for all patients, we cannot exclude some misdiagnosis. Particularly in some patients (those who underwent hepatitis B and other immunizations before the occurrence of complaints, those with a time interval of >1 month between the vaccination and the occurrence of complaints), the imputation may be considered as more doubtful. Moreover, our large series could be due to a recent French national campaign to encourage adolescents and young adults to receive hepatitis B vaccine. Following this campaign, a great number of subjects (including middle-aged subjects) received the vaccine and, at this time, >20 million French people have been vaccinated (but it is difficult to know exactly the total number of people immunized between 1992 and 1997). A number of these subjects would have developed rheumatic disorders if not vaccinated. Our national reporting system did not show any increase in the incidence of autoimmune disorders following hepatitis B immunization. This result is in favour of a coincidental relationship.

However, several arguments are in favour of a causal relationship. For a majority of patients, the temporal association was suggestive. The manifestations worsened in most of the patients who were given a further injection. In some patients, the complaints regressed after a few weeks or months, and did not recur during the follow-up. In most patients, the explorations and the follow-up did not show any other plausible cause for the complaints. Moreover, since patients with rheumatic disorders were not systematically questioned about prior immunization in the past years, and since the national reporting system of drug adverse effects is based not on obligatory but on voluntary notifications, the negative results from this reporting system do not exclude a link between immunization and some rheumatic disorders.

Large-scale immunization programmes have not established any association between vaccination and the occurrence of serious adverse effects [6, 7, 11]. However, systematic surveillance for adverse reactions in these populations was sometimes performed with questionnaires. Moreover, the number of subjects may not have been sufficient to detect a slight increase in the incidence of rheumatic disorders. Unfortunately, our work does not allow us to know the frequency of rheumatic disorders in people undergoing hepatitis B vaccination, and to know whether this frequency is different or not from that in other people. Because of the retrospective design, patients presenting in our departments were not systematically questioned about prior immunization.

Consequently, we do not know what percentage of patients seen in our departments during the period covered by the study developed symptoms following immunization. Moreover, we do not know how many patients developing musculoskeletal symptoms following hepatitis B immunization were treated by office-based rheumatologists or general practitioners during the time period covered by the study.

Consequently, at this time, there is a discrepancy between the negative results of epidemiological studies and the description of suggestive cases, including ours. Further epidemiological studies including a sufficient number of subjects to detect a slight increase in the relative risk are needed to establish whether hepatitis B vaccination is associated or not with an incidence of rheumatic disorders higher than normal.

On the other hand, the presumed risk for adverse events must be weighed against the expected risk for HBV-related liver disease [6]. Since the relative risk of occurrence of rheumatic complaints following hepatitis B vaccination is not or is slightly increased compared to the general population, the morbidity and mortality that can be prevented by immunization against hepatitis B outweigh by far the risk of possible adverse events [42]. Consequently, in our opinion, the possible rheumatic adverse effects do not put into question universal immunization. However, questions are raised about hepatitis B vaccine recommendation in some patients, especially those with chronic inflammatory or autoimmune diseases, and those with previously suspected adverse effects related to hepatitis B immunization. Studies are needed to respond to these questions.

In conclusion, hepatitis B vaccine might be followed by various rheumatic conditions and might trigger the onset of underlying inflammatory or autoimmune rheumatic diseases. However, a causal relationship between hepatitis B vaccination and the observed rheumatic manifestations cannot be easily established. Further epidemiological studies are needed to establish whether hepatitis B vaccination is associated or not with an incidence of rheumatic disorders higher than normal.

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